Drug Therapy, Green Chemistry and Design for Degradation Innovations to Reduce the Quantity of Drugs Entering the Environment

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Pharmaceutical Life Cycle

(**Covered in talk**)

- Research and Development
  - **Drug Discovery: Drug substance (molecular structure)**
  - **Synthesis development:** drug substance manufacturing
  - **Formulation development:** Pill, Capsule, IV, etc. manufacture
  - Preclinical, Metabolism, Clinical, Environmental studies
  - Drug Registration
- **Manufacturing – Drug Substance & Drug Product**
  - **Process re-development (new science and technology available)**
- Drug product distribution and reverse distribution
- Sales/Prescription
- Patient use - - **Metabolism/Excretion**
- End of life
  - Unused: Disposal
  - Used/excreted: Treatment**/Environmental fate and effects**

Drugs

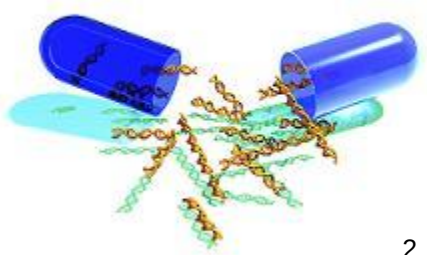
1. Small-molecules with precisely defined chemical structure
   - Active molecule typically manufactured by organic synthesis (series chemical reactions, in solvent)
   - Drug product (pill, capsule, intravenous) produced separately – different facility/equipment/operations

2. Biologics – Large molecules: proteins, peptides, or nucleic acids
   - Therapeutic proteins & vaccines - almost entirely produced by fermentation using microbial or mammalian cells
   - Peptides and oligonucleotides produced by chemical synthesis

Pharmaceutical Concentrations

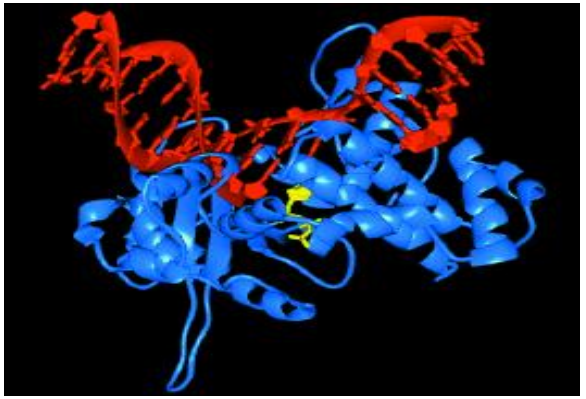
- Lower the environmental concentration the greater the environmental safety
- How accomplish lower concentrations?
  - Drug therapy innovations (patient driven: efficacy & side effects) - - dynamic field!
    - Personalized medicine
    - Biologics
    - Drug formulation – targeting & bioavailability
  - Green chemistry opportunities (sustainability and economics driven)
    - Manufacturing Operations
    - Design for Degradation

Drug Therapy Innovations



1. Personalized Medicine
   - Concept: Drug/dose selection matched to the genetics of a subpopulation of the patients with a medical condition
     - Objective: increase efficacy & decrease side effects
     - Environmental implications: less of an individual drug is used, less loading to the environment so lower environmental concentration, less risk potential
   - Status: Progress (Herceptin®) & Optimism
     - Science: Human genome mapped, other advances
     - Challenges:
       - Genetic/molecular markers of disease
       - Diagnostic tools for identifying subpopulations
       - Therapeutic options

Drug Therapy Innovations



2. Biologics

- Concept: Biological medicines (monoclonal antibodies, vaccines, gene therapies, therapeutic proteins) target disease with great specificity (a very good thing!)
  - Environmental implications: Natural molecules, do not persist
- Status: Substantial innovation
  - 633 biotechnology medicines in development in 2008(4)
  - 15 biologics included in the 34 new medicines FDA approved in 2009(5)

Example of Personalized Medicine & Biologics Breast Cancer Treatment with Herceptin®

1. Personalized Medicine[6]

- Approximately 30% of breast cancer cases are characterized by over-expression of a cell surface protein called human epidermal growth factor receptor 2 (HER2)
- For these patients, standard therapy is not effective, but an antibody drug called Herceptin® (trastuzumab) does work
  - Substantially reduces tumor recurrence in combination with chemotherapy
- Molecular diagnostic tests for HER2 identify the 30 percent of patients that will benefit from receiving Herceptin®
  - Drug prescribed to that 30% of patients rather than to a larger percentage

2. Biologics

- Herceptin® is protein based and will rapidly degrade in the environment[7]

Bioavailability

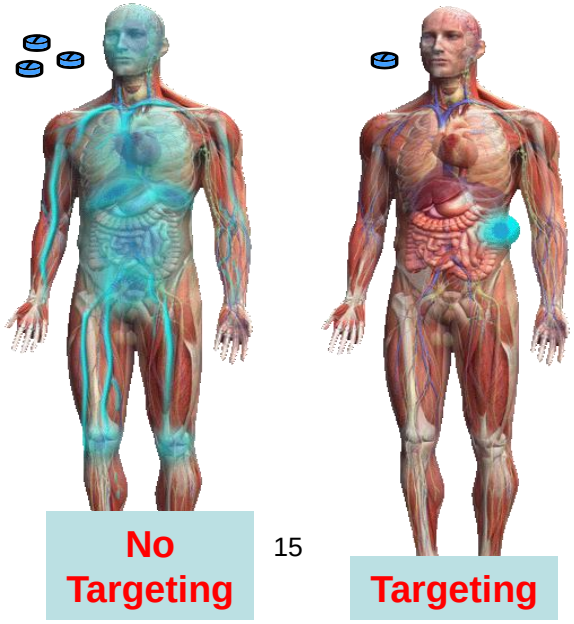
- Bioavailability - the fraction of an administered dose of drug that reaches the systemic circulation

- Cue [13A] highlighted that 80-85% of drugs have poor oral availability
  - Lipitor, for example, is only 12% bioavailable
  - Doubling bioavailability would halve the level of drug entering the environment

Drug Therapy Innovations

3. **Formulation**

- Concept: Use formulations to improve bioavailability and/or target a location in the body
- Increase efficacy, reduce side effects, minimize use & environmental load
- Examples of approaches to affinity and bioavailability:
  - Nanotechnology*
  - Conjugates/prodrugs (ex, rifamycins)
  - Drug Particle Size Optimization



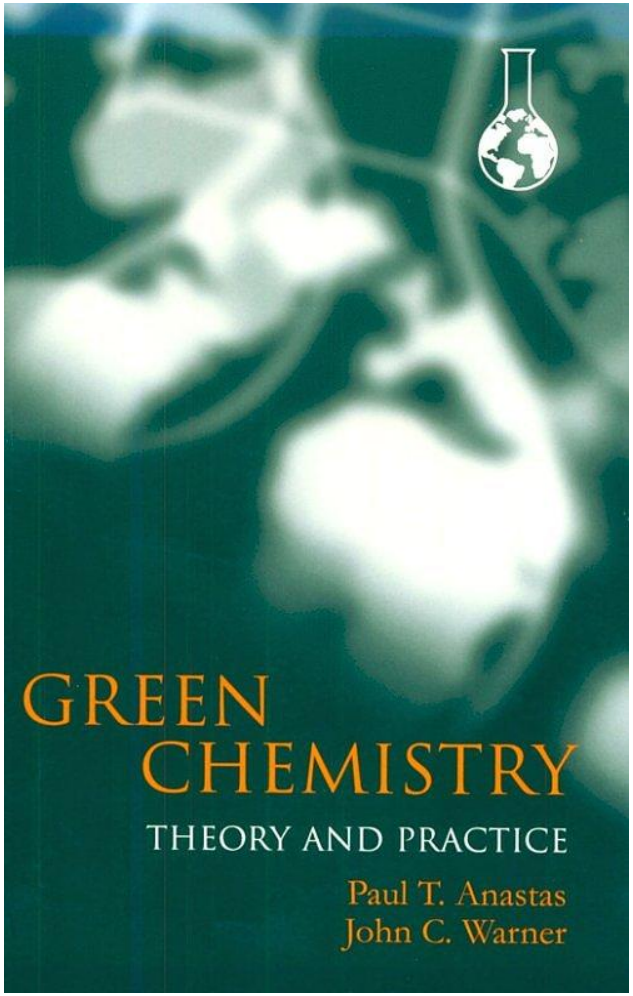
* Nanotechnology - environmental toxicity an emerging area of concern and research[14]

- Status: Current applications; innovation, especially nanotechnology to improve bioavailability of existing drugs

Formulation Example Bisphosphonate Prodrugs[16]

- Osteomyelitis – a bone infection
  - Treatment often requires surgery and prolonged antibiotic therapy
  - New class of prodrugs developed: rifamycins are linked to a bisphosphonate with high affinity for bone tissue
  - Antibiotics are delivered directly to infection site, where they are concentrated to exert therapeutic activity

What is Green Chemistry?



"…the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products."[10]

The Twelve Principles of Green Chemistry

✓ 1. **Prevent waste:** Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.

✓ 2. **Design safer chemicals and products:** Design chemical products to be fully effective, yet have little or no toxicity.

✓ 3. **Design less hazardous chemical syntheses:** Design syntheses to use and generate substances with little or no toxicity to humans and the environment.

4. **Use renewable feedstocks:** Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.

5. **Use catalysts, not stoichiometric reagents:** Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.

6. **Avoid chemical derivatives:** Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.

Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998).

The Twelve Principles of Green Chemistry

7. **Maximize atom economy:** Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.

8. **Use safer solvents and reaction conditions:** Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.

9. **Increase energy efficiency:** Run chemical reactions at ambient temperature and pressure whenever possible.

✓ 10. **Design chemicals and products to degrade after use:** Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.

11. **Analyze in real time to prevent pollution:** Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.

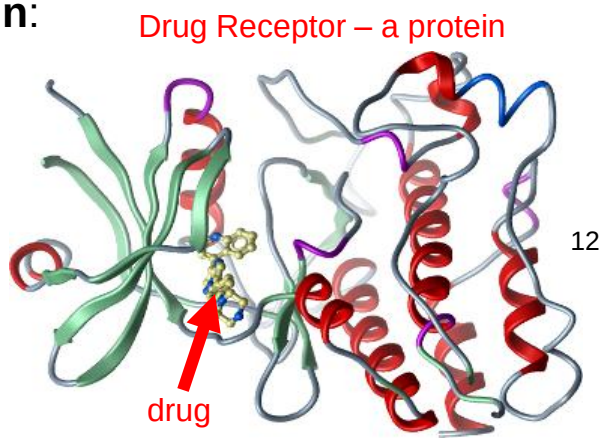
12. **Minimize the potential for accidents:** Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment

Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998).

Drug Discovery

Design for Degradation (Green Chemistry Principle # 10)

- Concept: Drug designed to degrade after use, innocuous products
- Status: Challenging scientific problem, limited investment[13]
  - Drugs must have a **chemical structure that results in**:
    - Bioactivity = binding with a target in the body
    - Acceptable safety profile
    - Stability in synthesis, formulation, storage, use



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- BUT, then we want the drug to switch to unstable, which is **also a function of structure**
- Dilemma: Currently lack the scientific knowledge to achieve BOTH the necessary drug properties and instability following efficacy. Mechanisms of degradation can be same internally and in the environment

Existing vs. New Drugs

- Opportunities to advance DfD:
  - **Develop a structure/environmental toxicity screen to inform drug discovery early, when 1,000's of molecules are evaluated**
  - **Approach to designing potentially problematic drugs to achieve "instability" once in the environment – chemist creativity**

Additional info re: Design for Degradation (DFD)

- Book Chapter:
  - **“Environmental Science and Green Chemistry; guiding business success through environmentally preferred manufacturing and chemical product design”**
  - Authors: Richard T. Williams and Travis R. Williams
  - Pharmaceutical/Biologics and Nanotechnology case studies
  - Design for Degradation covered, including:
    - Market Forces, Business case, incentives
    - Approaches and Environmental decision making tools: existing and needed
- Upcoming Presentation:
  - **15th Green Chemistry and Engineering Conference Jointly held with the 5th International Conference on Green and Sustainable Chemistry, June 21-23, 2011, Washington DC**
    - **Session: Greener Pharmaceutical Processes and Products (Cue/Williams)**
    - **Talk: Williams – Greener products, design for degradation rationale, approach**

Green Chemistry

1. Drug Substance Manufacturing (Synthesis)

- Concept: (Re)Design drug synthesis to minimize material/energy/water use and waste generation
- ACS Green Chemistry Institute, Pharmaceutical Roundtable – id rxn needs, grant money, publications
- Pharmaceutical companies have won 9 US EPA Presidential Green Chemistry Challenge Awards
- Example from US EPA Presidential Green Chemistry Challenge Awards:
  - Roche Colorado, antiviral Cytovene®: Eliminated ~ 2.5 million lbs of hazardous liquid waste and > 55,000 pounds of hazardous solid waste each year [18]

Example: Pregabalin enzymatic **synthesis** – benefits[28]

- Between 2007 and 2020 the new synthesis will eliminate:
  - 185,000 tonnes of solvent, > 90 % reduction
  - 4,800 tonnes of mandelic acid, a 100 % reduction
  - 2,000 tonnes of Raney nickel catalyst, a 90 % reduction
  - 15,000 tonnes of starting material, > 50 % reduction
- Latest Process uses > 7 times fewer inputs than the product launch route
- Energy usage reduced by 83%
- Solvent and Energy savings are the equivalent to saving 413,550 tonnes of CO_2 emissions
  - Equivalent to taking 69,000 US cars off the road for a year!

Green Chemistry

Greener Drug **Synthesis** – Summary

- Examples of Success are Powerful and Important
- Extent to which green process chemistry manufacturing initiatives (drug synthesis) have minimized the release of active drug to wastewater and the environment not clear
  - Active drug only present in final step(s) of the synthesis pathway (series of reactions)
  - Final process step may be carried out in an organic solvent – no wastewater

Green Chemistry

2. Drug Product Manufacturing

   Formulation (incorporating the drug substance into a pill, capsule, etc.)

   – US Geological Survey publication June 2010, US pharmaceutical formulation facility (PFF) discharges [21]

   - "findings suggest that current manufacturing practices at these PFFs can result in pharmaceuticals concentrations from 10 to 1000 times higher than those typically found in WWTP effluents"

   – Status: findings from effluents of 2 WWTP receiving PFF wastewater
   - How representative of US pharmaceutical formulation facilities (PFF)?
   - Possible source: equipment (blenders, etc.) cleaning operations using water/cleaning agents

   – Opportunity:
   - Apply green chemistry principles to drug formulation manufacturing operations (cleaning technology, handling)

Moving Forward - 1

- Drug therapy innovations can benefit patients and the environment
- Green Chemistry is:
  - An economical[26] and proven solution for greener drug substance (**synthesis**) manufacturing (for biologics, green chemistry applications being explored)
  - A tool for greening drug **formulation** manufacturing
  - A research opportunity for greener drug design
- Scholarship and innovation needs:
  - Rapid and early feedback on the environmental properties of drug candidates based on structure that indicate potential risks - environmental science!
  - How to design and/or formulate less stable drugs when environmental risks are significant – design features (structural) that are preferred – environmental science!

Moving Forward – 2
Drug Design Principles

- There are chemical principles for designing effective drugs[27]
- BUT there are no design rules that facilitate innovation/creativity by design chemists for avoiding potentially problematic attributes or including preferred attributes (or) addressing (formulation, etc.) drugs that may be environmentally problematic - - ALL during the early phases of research, before a drug structure or formulation is finalized

Implications to PPCP Mgmt

- Drug Therapy: Value/support science – innovation and incentives
  - Long haul and yes, it is hard
- Water Quality
  - Domestic wastewater is not for disposal of unused medicine
  - Make unavoidable “contaminants” safer / degradable – from the start to extent possible (reduce need for assimilation)
- Informed prioritization for green chemistry initiatives - objective criteria
- Innovation over regulatory imperatives (but…)
  - Incentives, collaboration, innovation
  - Good science

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Rich holds a Ph.D. in ecology with an emphasis on biodegradation and aquatic ecosystems, having trained at the University of Minnesota Limnological Research Center, Freshwater Biological Institute, and Lake Itasca Biology Station. In his current position as president of Environmental Science & Green Chemistry Consulting, Rich authored a chapter describing environmental decision-making tools and green chemistry approaches to achieving more preferred products and manufacturing processes. In addition, he briefed the US Congress on green chemistry as mitigation for pharmaceuticals in the environment (PIE) and consults with industry and government clients. He previously worked at Pfizer*, and selected experiences are bulleted below. He managed an environmental fate and effect lab for Weston and worked at Harvard Medical School in immunology earlier in his career.

Experience with pharmaceuticals includes:

- 17 years of environmental science and green chemistry experience at Pfizer* Global R&D. Managed the development of environmental risk assessments for drugs to support marketing applications.
- Co-founded and chaired the Pfizer Groton Green Chemistry team for 4 years, co-authoring a US Presidential Green Chemistry award winning nomination
- Chair, SETAC Pellston Workshop Steering Committee, addressed the adequacy of the existing science to identify risks and the environmental impacts of pharmaceuticals as contaminants
- Chair, Pfizer Pharmaceuticals in the Environment Leadership Team
- Member, Pfizer Nanotechnology Safety Practice Network
- Chair, Environmental Risk Assessment Team, Pharmaceutical Research and Manufacturers of America (P*h*RMA)
- Editor. *Human pharmaceuticals: assessing the impacts on aquatic systems*. SETAC Press; 2005:368p
- Organizing committee and opening speaker, Human Health Risk Assessment for Pharmaceuticals in the Environment, Society of Toxicology, Seattle, March 2008
- Member of a team that established a publicly available environmental classification system for pharmaceuticals in Sweden
- Founding chair of Society of Environmental Toxicology and Chemistry (SETAC) Pharmaceuticals Advisory Group
- Program Committee and keynote speaker for a drug registration EA conference: DIA/HESI/SAPS Workshop on Environmental Assessment of Human Medicines, Stockholm, May 22-23, 2006

*, Opinions expressed in this talk are those of Richard Williams, not those of Pfizer, and are not based on Pfizer proprietary information

References / Sources - 1

1. Williams & Cook (2007). Drug Information Journal, 41 (2) 133-142
2. Image: D. Hamilton. From VentureBeat published Sept 28, 2007. Accessed Sept 1, 2010. http://venturebeat.com/2007/09/28/big-pharmas-personalized-medicine-consortium-is-it-for-real/
3. Image: B. Fisher. From NIEHS News published Aug 8, 1999. Accessed Sept 1, 2010. http://ehp.niehs.nih.gov/realfiles/docs/1999/107-8/niehsnews.html
4. Biotechnology Medicines in Development. Pharmaceutical Research and Manufacturers of America (P*h*RMA). 2008. P*h*RMA website http://www.phrma.org/files/attachments/Biotech%202008.pdf
5. New Drug Approvals in 2009. Pharmaceutical Research and Manufacturers of America (P*h*RMA). 2010. P*h*RMA website http://www.phrma.org/sites/phrma.org/files/attachments/NDA_2009.pdf
6. Herceptin® example, Personalized medicine example: http://www.ageofpersonalizedmedicine.org/)
7. Biologics example, Herceptin®: Genentech Material Safety Data Sheet http://ctep.cancer.gov/branches/pmb/msds/688097-Trastuzumab_Herceptin_September_24_2004.pdf
8. Hormones Degrade in the Environment! USGS website: http://toxics.usgs.gov/highlights/hormones_degrade.html
9. Image: bacteria, from http://commons.wikimedia.org/wiki/File:Bacteria_photomicrograph.jpg
10. Green Chemistry Theory and Practice. P. Anastas and J. Warner. 1998. Oxford University Press.
11. Image: Light switch. From The Encyclopedia of Alternative Energy and Sustainable Living. Accessed Sept 1, 2010. http://www.daviddarling.info/encyclopedia/W/AE_when_to_turn_off_lights.html
12. Image: Ligand/receptor binding. Chaikuad et al., SGC website. May 8, 2010. Accessed Sept. 2, 2010. http://www.thesgc.org/structures/structure_description/3MY0/
13. Source: David Taylor, wca environment, 2nd International Conference on Sustainable Pharmacy: Incentives and perspectives – Osnabruck 2010
14. National Nanotechnology Initiative (NNI). NNI Environmental, Health, and Safety Research website http://www.nano.gov/html/society/EHS.html Accessed Sept. 2, 2010.
15. Image: Drug Targeting. Modified and used with permission of B. Cue.
16. Example, Bisponsponate drugs Reference: *A new approach towards the prevention and treatment of osteomyelitis: synthesis and in vitro studies of bisphosphonated rifamycin prodrugs.* Kang T et. al., 18th European Congress of Clinical Microbiology and Infectious Diseases. Barcelona, Spain, 19–22 April 2008 *Abstract number: O489*
17. Source: B. Cue, 2010 ACS meeting presentation, Boston, MA.

References / Sources - 2

18. Source: US EPA Presidential Green Chemistry Challenge website: http://www.epa.gov/gcc/pubs/pgcc/winners/gspa00.html
19. Image: ACS Green Chemistry Institute logo. Used with ACS permission. From ACS GCI website
20. Image: pharmaceutical blender. provided courtesy of and used with the permission of Mork Process, Inc., Stow, Ohio. Company website: http://www.mork-clean-in-place.com/
21. P. Phillips et al., 2010. Environ. Sci. Technol. 44:4910-4916. (June, 2010)
22. Image: US EPA. Accessed Sept 7, 2010. http://water.epa.gov/action/advisories/drinking/dwstandards.cfm
23. Image: Municipal WWTP. http://www.dyersburgtn.gov/water_treatment/wastewater_treatment_plant.htm
24. W. Solley et al., 1998. Estimated use of water in the US in 1995. US Geological Survey (USGS) Circular 1200.
25. US EPA's Sustainable Water Infrastructure initiative. http://water.epa.gov/infrastructure/sustain/index.cfm
26. ACS GCI website posting: "Pharma goes green to cut costs" Accessed Sept 2, 2010. http://www.rsc.org/chemistryworld/News/2008/July/09070801.asp
27. Lipinski reference Reference:C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings*, Adv. Drug Del. Rev., **2001**, *46*, 3-26. (DOI:10.1016/S0169-409X(00)00129-0
28. Pregabalin (Lyrica®) slides provided and approved for use by Dr. Peter Dunn, Pfizer

13A S. Everts, Greener drugs: benign-by-design strategies, *Chem. Eng. News*, **88,** 23-24, March 29, 2010.